UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/373,333	08/12/99	SUBRAMANIAN V	0113.004

HM12/0129

MAXYGEN INC
INTELLECTUAL PROPERTY DEPARTMENT
515 GALVESTON DRIVE
REDWOOD CITY CA 94063

EXAMINER	
JOHANNSEN, D	
ART UNIT	PAPER NUMBER
1655	19

DATE MAILED: 01/29/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/373,333	Applicant(s) Subramanian et al
	Examiner Diana Johannsen	Group Art Unit 1655

☒ Responsive to communication(s) filed on *Nov 13, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-60* is/are pending in the application.

Of the above, claim(s) *38-60* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-37* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4, 7, 9, 14*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of Group I, claims 1-37, in Paper No. 16 is acknowledged.

2. Claims 38-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Sequence Listing

3. It is noted that the Scientific and Technical Information Center made the following corrections to the computer readable form of the Sequence Listing: non-ASCII "garbage" at the end of files was deleted.

Claim Objections

4. Claim 13 is objected to because of the following informalities: item "(b)" should be followed by "and", such that the claim will recite a proper Markush group. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-37 are indefinite for failing to recite a final process step that clearly relates back to the claim preamble. The claims are drawn to a method "of obtaining a recombinant herbicide tolerant nucleic acid which can confer tolerance to an herbicide upon a plant", yet recites a final process step of screening a library "to identify at least one recombinant herbicide tolerance nucleic acid" that encodes an activity "which confers herbicide tolerance to a cell". The claims do not set forth how screening to identify a nucleic acid "which confers herbicide tolerance to a cell" will result in obtaining a nucleic acid that "can confer tolerance to an herbicide upon a plant". Accordingly, it is unclear as to whether the claims are intended to be drawn to methods of obtaining nucleic acids that confer tolerance upon plants, or methods of screening in which nucleic acids that "confer herbicide tolerance" to a "cell" are "identified". It is further noted that as the claims do not require a step of, e.g., assaying a plant for herbicide tolerance, it is unclear as to how one would conclude that a nucleic acid "can confer tolerance" to a plant. Clarification is required.

Claims 1-37 are indefinite over the recitation of the term "obtaining". It is unclear as to what is meant by this language. For example, would a "method of obtaining" a nucleic acid

require one to isolate or separate that nucleic acid, or would mere detection in a population be sufficient to accomplish "obtaining"? Clarification is required.

Claims 1-37 are indefinite over the recitation of the term "derived". As any nucleic acid may be manipulated or "derived" so as to prepare any other nucleic acid, it is unclear as to how the recitation of the limitation "segments derived from the parental nucleic acid" is intended to further limit the claims. Clarification is required.

Claims 1-37 are indefinite over the recitation of the language "nucleic acid encodes ...activity". As the term "encodes" is known in the art to refer to a particular relationship between nucleic acids and proteins, rather than nucleic acids and "activities", it is unclear as to what is intended to be encompassed by this language. Particular, it is unclear as to whether the use of the term "encodes" in the claims is intended to limit the claims to nucleic acids encoding proteins having herbicide tolerance activity, or whether the claims are intended to encompass nucleic acids that might influence herbicide tolerance in other ways. Clarification is required.

Claims 1-37 are indefinite over the recitation of the phrase "wherein the plurality of variant forms differ from each other in at least one nucleotide". It is unclear as to what is meant by this language. For example, is this language intended to refer to, e.g., a mutation or polymorphism at a particular position in a gene, or is some other type of "difference" (e.g., in the types of nucleotides present in the "variant forms") suggested by this language? Clarification is required.

Claims 1-37 are indefinite over the recitation of the term "identify". It is unclear as to what is encompassed by this term. For example, would detection of a molecule possessing a

particular property be sufficient to accomplish "identification", or is further characterization of a nucleic acid required to "identify" it? Additionally, it is noted that the terms "identify" and "identifying" are sufficiently broad so as to so as to encompass solely mental steps of "identification". The claims should be amended so as to clearly set forth the active process steps necessary to carry out the claimed methods.

Claim 30 is indefinite because it is unclear as to how the claim is intended to further limit claim 1, from which it depends. For example, are the steps recited in claim 30 intended to be performed in addition to or instead of one or more of the steps of claim 1? The claim should be amended so as to clarify how the steps of claim 30 relate to those of claim 1.

Claim Rejections - 35 U.S.C. § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-7, 9-10, 12-20, 23-33, and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khosla et al (U.S. Patent No. 5,521,077 [5/1996]) in view of Subramanian et al (J. Industrial Microbiol. & Biotechnol. 19:344-349 [1997]).

Khosla et al teach a method termed "recombination-enhanced mutagenesis" in which "large populations of protein variants" are produced *in vivo* by recombination of multiple sets of allelic variants (see entire reference, especially, e.g., col lines 8-14, col 2, lines 5-64). Khosla et al disclose methods in which steps of recombining "variant forms" *in vivo* to produce a recombinant library are followed by a step of screening recombinants for proteins having desired activities (see, e.g., col 2, lines 57-61; col 4, lines 51-58; col 6, line 64-col 7, line 10; Fig. 1). Khosla et al state that recombinants generated by their methods can be "subjected to selection or screening by any appropriate method depending on the sought after characteristic or property of the protein of interest, for example, enzymatic or other biological activity, binding to a receptor molecule, inhibition of the binding of another receptor ligand, or the like" (col 7, lines 5-10). However, Khosla et al do not teach or suggest employing their method to obtain or identify nucleic acids encoding an activity "which confers herbicide tolerance" to a cell, as required by the claims. Subramanian et al disclose that herbicide tolerance is desirable in crops, and disclose that genes conferring herbicide tolerance may be incorporated into plants (see entire reference, especially p. 344). Subramanian et al further disclose that it is beneficial for plants to contain multiple

herbicide-metabolizing enzymes (p. 344). Finally, Subramanian et al teach methods of screening for new enzymes that confer herbicide tolerance (see, e.g., p. 347), and teach that the identification of novel genes conferring tolerance is beneficial because it provides "more options" for use in transgenic crops (p. 344). In view of the teachings of Subramanian et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the "recombination-enhanced mutagenesis" method of Khosla et al so as to have recombined variant forms of nucleic acids encoding activities that confer herbicide tolerance and screened the resultant recombinant libraries for herbicide tolerance. Subramanian et al clearly disclose that the property of herbicide tolerance constitutes, using the language of Khosla et al set forth above, a "sought after characteristic or property". Further, the teachings of Subramanian et al reveal a need for multiple, novel, variant genes that can be used to confer tolerance to crops, and Khosla et al disclose that their "recombination-enhanced mutagenesis" method permits efficient preparation of large, high quality populations of recombinants for screening (see, e.g., col 2, lines 5-61). Accordingly, an ordinary artisan would have been motivated to have modified the method of Khosla et al for the advantage of rapidly and efficiently identifying novel nucleic acid variants encoding activities conferring herbicide tolerance.

With respect to claim 2, it is a property of Khosla et al's method that it results in the preparation of recombinant molecules that are "distinct" as "compared to the parental nucleic acid". With respect to claims 3 and 4, it is noted that the combined teachings of Khosla et al and Subramanian et al are sufficient to suggest methods in which "parental nucleic acids" either have

or lack "herbicide tolerance activity". With respect to claim 5, Subramanian et al disclose that herbicide tolerance may result from altered target proteins (Table 1), and thereby suggest the use of parental nucleic acids encoding such proteins in the method of Khosla et al in view of Subramanian et al. With respect to claim 6, Khosla et al teach the use of allelic variants of "parental" nucleic acids in their methods (see, e.g., col 2, lines 33-38). With respect to claim 7, Khosla et al disclose the preparation of a plurality of variants that would be homologous to the "parental nucleic acid" (col 5, lines 11-44). With respect to claims 9-10, and 12, Subramanian et al disclose a variety of herbicide tolerance conferring genes, including bacterial genes encoding 5-enol-pyruvylshikimate-3-phosphate synthase, phosphinothricin acetyl transferase, and glyphosate oxidoreductase, and a plant gene encoding acetolactate synthase (Table 1). With respect to claim 14, the libraries taught by Khosla et al are present in a "population of cells", as required by the claims. With respect to claims 13 and 15-17, Subramanian et al disclose a variety of methods of screening for herbicide tolerance, including screening a population of cells for oxidation of dicamba (see, e.g., Fig. 2 and Fig. 3). With respect to claims 18-20, Subramanian et al teach screening by assaying for growth in media comprising the herbicide of interest (p. 347). With respect to claim 23, Subramanian et al disclose that it is beneficial for plants to contain multiple herbicide-metabolizing enzymes (p. 344), and thereby provide motivation to screen for multiple herbicide tolerance activities. With respect to claim 24, the recombining step taught by Khosla et al requires a "plurality of cells" (see, e.g., col 2, lines 30-64). With respect to claims 25-29, Khosla et al disclose that repetition of their methods may be used to generate additional, distinct

recombinant molecules (see, e.g., col 7, lines 11-23). With respect to claim 30, Khosla et al teach performance of their methods using bacterial cells (see, e.g., claim 16). With respect to claim 31, Subramanian et al disclose a variety of mechanisms of herbicide tolerance, including, e.g., rapid metabolism of herbicides (see entire reference). With respect to claims 32-33, Subramanian et al discloses that herbicide tolerance genes can be transduced into plants as a means of improving crops, and disclose that herbicide tolerance proteins should function "in a plant environment", thereby providing motivation to screen transgenic plants for herbicide tolerance (p. 344). With respect to claims 35-37, it is a property of the recombinant libraries prepared by the methods of Khosla et al in view of Subramanian et al that they would constitute recombinant libraries and comprise recombinant "herbicide tolerance" nucleic acids.

9. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Khosla et al in view of Subramanian et al as applied to claims 1-7, 9-10, 12-20, 23-33, and 35-37, above, and further in view of Krebber et al (U.S. Patent No. 5,514,548 [5/1996]).

While Khosla et al teaches that mutagenesis of "parental" nucleic acids may be "accomplished by several different techniques known in the art" (col 5, lines 27-44), the combined references of Khosla et al and Subramanian et al do not teach or suggest producing variant forms of a parental nucleic acid by error-prone transcription or by replication in a mutator strain, as required by the instant claim. Krebber et al disclose that mutagenesis may be performed by a variety of methods, and specifically teach that propagation in mutator strains may be used to perform mutagenesis and results in "increased mutation rates". In view of the teachings of

Krebber et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Khosla et al in view of Subramanian et so as to have performed mutagenesis of parental nucleic acids by propagating those nucleic acids in a mutator strain. First, as Khosla et al suggest that a variety of mutagenesis methods may be employed successfully in their methods, an ordinary artisan would have been motivated to have employed in the method of Khosla et al in view of Subramanian et al any step that could conveniently be performed to accomplish mutagenesis, including propagation in a mutator strain (i.e., one would have been motivated to have selected this method in instances in which mutator cell lines were readily available, for the advantage of convenience). Additionally, as Krebber et al teaches that propagation in mutator cell lines results in "increased mutation rates", an ordinary artisan would have been further motivated to have employed this method for the advantage of rapidly generating populations of allelic variants.

10. Claims 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khosla et al in view of Subramanian et al as applied to claims 1-7, 9-10, 12-20, 23-33, and 35-37, above, and further in view of Padgette et al (Herbicide-Resistant Crops, Duke, S.O., ed., CRC Lewis Publishers, Boca Raton, pp. 53-84 [1996]).

The combined references of Khosla et al and Subramanian et al do not teach or suggest the use of Mpu+ or AroA- bacteria, or teach or suggest "herbicide tolerance" nucleic acids that encode "an activity that catalyses the conversion of glyphosate to aminomethylphophonate" or

"an activity which catalyses the conversion of phophoenolpyruvate plus shikimate 3-phosphate to 5-enolpyruvylshikimate-3-phosphate".

With respect to claim 21, Padgette et al disclose that one mechanism of glyphosate tolerance results from degradation of glyphosate to aminomethyl phosphate (AMPA) (p. 56), and disclose that Mpu+ bacteria utilize methylphosphonate (see, e.g., p. 69). In view of the teachings of Padgette et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Khosla et al in view of Subramanian et al so as to have identified "glyphosate tolerance" nucleic acids by employing parental nucleic acids variants of genes that convert glyphosate to AMPA and Mpu+ bacteria in screening for nucleic acids that catalyze the conversion of glyphosate to AMPA. An ordinary artisan would have been motivated to have made such a modification for the advantage of identifying novel variants of genes that confer glyphosate tolerance for use in transgenic crops. Further, as Padgette et al disclose that Mpu+ bacteria utilize methylphosphonate, an ordinary artisan would have been motivated to have employed such bacteria for the advantage of allowing rapid screening based on the growth on glyphosate as a phosphorus source.

With respect to claim 22, Padgette et al teach that mechanisms of glyphosate tolerance include overproduction of EPSPS and "introduction of an EPSPS with decreased affinity for glyphosate" (p. 56), and disclose that AroA- bacteria lack EPSPS activity (see, e.g., p. 60). In view of the teachings of Padgette et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Khosla et al in

view of Subramanian et al so as to have identified "glyphosate tolerance" nucleic acids by employing parental nucleic acids variants of EPSPS genes and AroA- bacteria in screening for nucleic acids that possess EPSPS activity. An ordinary artisan would have been motivated to have made such a modification for the advantage of identifying novel variants of EPSPS that confer glyphosate tolerance for use in transgenic crops. Further, as Padgette et al disclose that AroA- bacteria lack EPSPS activity, an ordinary artisan would have been motivated to have employed such bacteria for the advantage of allowing rapid screening based on the presence of EPSPS activity in recombinant cells.

11. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Khosla et al in view of Subramanian et al as applied to claims 1-7, 9-10, 12-20, 23-33, and 35-37, above, and further in view of Aono et al (Plant Cell Physiol. 36(8):1687 [1995]).

While the combined references of Khosla et al and Subramanian et al suggest screening preparing transgenic plants comprising recombinant herbicide tolerance nucleic acids, the combined references do not teach or suggest breeding such plants "with a separate plant strain of the same species, followed by selection of resulting offspring for tolerance to the herbicide". Aono et al disclose that breeding of plants possessing different tolerance genes may be used to prepare plants having multiple mechanisms of herbicide tolerance (see, e.g., p. 1688). Accordingly, in view of the teachings of Aono et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Khosla et al in view of Subramanian et al so as to have cross fertilized plants possessing different

tolerance mechanisms for the advantage of preparing improved crops having multiple mechanisms of tolerance, as suggested by Aono et al.

Drawings

12. It is noted that the drawings have been approved by the Draftsperson.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday from 7:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at 703/308-1152. The fax phone number for the Technology Center where this application or proceeding is assigned is 703/305-3014 or 305-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana Johannsen

January 25, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

1/26/01